Preliminary report of a toxicity study of hydroxyurea in sickle cell disease

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Abstract

***Aim*—To evaluate the tolerance of hydroxyurea in children affected with sickle cell disease.**

***Design*—Questionnaire study of French physicians likely to treat patients with sickle cell disease. Data were collected on 101 children with sickle cell disease, treated for a median of 22 months, 36 of whom were treated for more than three years. 13 children were younger than 5 years of age at inclusion.**

***Results*—Hydroxyurea was stopped for medical reasons in 11 patients: 6 failures, 1 pregnancy, 1 cutaneous rash, 1 leg ulcer, 1 lupus. Acute lymphoblastic leukaemia occurred in a girl treated for 1.5 months with hydroxyurea, this short interval arguing against a causative association. One 17 year old boy had paraparesis after 8 years of treatment.**

***Conclusions*—No major short or medium term toxicity was related to hydroxyurea in this cohort of 101 children. However, the number of children treated for more than 3 years is too few to make firm conclusions on the long term tolerance of this drug.**

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Hydroxyurea can drastically reduce the number of painful episodes in children affected with sickle cell disease,[1–6] restoring the quality of life for children afflicted by recurrent pains. It has been suggested that the efficacy of the drug could be even greater in children than in adults.[7] Because hydroxyurea is cytotoxic and cytostatic, its use was initially restricted to children with the most severe pain, for whom the therapeutic effect counterbalanced uncertainties about possible long term toxicity. The question now arises of whether to use hydroxyurea in infants to prevent organ dysfunction.[8] It has been shown that hydroxyurea has pleiotropic effects, not only inhibiting polymerisation of deoxyhaemoglobin S, in relation to the reactivation of haemoglobin F synthesis, but also decreasing the expression of adhesion molecules on reticulocytes.[9] Both effects could prevent the generalised vasculopathy seen in the severe forms of the disease. Clearly, widening the indications for hydroxyurea treatment requires more data about its tolerance in children with sickle cell disease. There have been few reports on long term hydroxyurea use in children.[10] The reassuring data provided by Triadou and colleagues[10] led us in 1992 to implement a paediatric protocol in France.[4 7] We report our findings regarding tolerance of hydroxyurea in a cohort of 101 children, 36 of whom had been treated for more than three years.

Methods

A treatment protocol for children with sickle cell disease who had suffered at least three vaso-occlusive painful crises necessitating hospitalisation in the year before entering the study was begun in France in 1992. First, extensive clinical and laboratory results were recorded for 35 children, on both efficacy and tolerance of hydroxyurea. This supported previous findings of its efficacy in painful crises.[4 7] After this initial study period ended, we focused on studying the tolerance to this drug. Because patients were no longer under a centralised protocol, we decided to send a questionnaire to all French physicians likely to have children with sickle cell disease under their care, to record any side effects related to hydroxyurea treatment. Forms were completed annually by physicians, whether or not they had observed an adverse event. The last evaluation, in September 1998, gave tolerance data for 101 children.

Results

Ninety nine children were homozygous SS, one had S-β^0 thalassaemia and one had a S-β^+ thalassaemia. There were 55 boys and 46 girls. Their mean (SD) age when starting hydroxyurea was 9.8 (0.4) years (range, 2–20). Thirteen children were less than 5 years old at inclusion. One child had anti-HIV antibodies. Mean (SD) daily dose was 21.4 (0.5) mg/kg/day (range, 9–30). Hydroxyurea was initially given on four days each week; administration protocols varied thereafter (four, five, six days each week, or every day).

For the 101 children registered, the mean duration of treatment in September 1998 was 22 months (range, 10 days to 93 months). Table 1 gives the lengths of treatment. Three children were lost to follow up after 23, 46, and 63 months of treatment, respectively.

Table 1 Duration of treatment

Months (n)	*Patients (n)*
1–12	23
12–24	33
24–36	9
36–48	14
48–60	8
60–72	6
72–84	6
84–96	2

STOPPING HYDROXYUREA

Hydroxyurea was stopped in 17 children, for reasons indicated in table 2. Of the six failures, one was confirmed after six months of treatment, the child having never responded either clinically or according to laboratory investigations. In the five other cases, a clinical benefit was observed initially, but treatment

Table 2 Reasons for stopping hydroxyurea treatment in 17 children with sickle cell disease

Reasons	*n*	*Hydroxyurea treatment (months)*
Failure	6	6, 22, 22, 40, 52, 53
Moving from town	2	12, 14
Non-compliance	1	46 (death post-BMT)
Pregnancy	1	50
Cutaneous rash	1	10 days
Leg ulcer	1	23
Lupus	1	12
ALL	1	1.5
No explanation	3	12, 22, 45

ALL, acute lymphoblastic leukaemia; BMT, bone marrow transplant.

was subsequently discontinued because of the recurrence of painful crises. Four of these five children are now receiving monthly exchange transfusions.

After non-compliance with hydroxyurea treatment, allogenic bone marrow transplantation was performed in an 8 year old boy, who died in the days after transplantation. A 19 year old girl became pregnant after receiving hydroxyurea for 50 months, although it had been cleary explained to her that she should take an oral contraceptive. She gave birth to a healthy child. Two events led to cessation of hydroxyurea treatment because of a possible adverse effect: a cutaneous rash observed 10 days after beginning treatment, and a leg ulcer observed in an 18 year old patient after 23 months of treatment. However, two other major events that occurred in children receiving hydroxyurea were probably not linked to this agent. As previously reported, one 13 year old girl developed renal failure after being treated with hydroxyurea for one year.[4] Serological and histological tests indicated a lupus erythematosus syndrome, likely to be coincidental. Lastly, hydroxyurea was stopped after 1.5 months in a 10 year old girl with the SS genotype. This patient had been affected for several years with painful bone crises up to three to seven times each year; these became much worse in May 1997. Hydroxyurea was begun on 3 June 1997 (17 mg/kg/day). Her initial blood count showed: 27 000/mm^3 leucocytes (neutrophils, 42%; lymphocytes, 42%; monocytes, 7%; eosinophils, 8%; basophils, 1%); haemoglobin, 104 g/l; erythroblasts, 11%; reticulocytes, 602 000/mm^3; platelets, 595 000/mm^3. She was admitted to hospital on 29 July 1997 for pain and fever. Her blood count showed: leucocytes, 40 000/mm^3 (neutrophils, 9%; lymphocytes, 26%; monocytes, 2%; myelocytes, 3%; blasts, 60%); haemoglobin, 56 g/l; reticulocytes, 100 000/mm^3; platelets, 151 000/mm^3. Bone marrow examination disclosed acute lymphoblastic leukaemia, with evidence of Philadelphia chromosome. Hydroxyurea was stopped. Chemotherapy induced a complete remission, sustained one year after induction, and she no longer suffers from bone pains.

TEMPORARY CESSATIONS OF TREATMENT

Some haematological adverse events occurred and resolved after temporary cessation or a decrease in the dose of hydroxyurea given, namely: neutropenia (five cases, two between 500 and 1500/mm^3; three between 1000 and 1500/mm^3); thrombocytopenia (four cases between 90 000 and 100 000/mm^3); reticulocytopenia (five cases between 80 000 and 90 000/mm^3).

Hydroxyurea was also temporarily stopped in a 17 year old boy with the SS genotype, while considering the possible responsibility of the drug for a neurological manifestation. This boy had a history of left hemiplegia and aphasia when he was 7 years old. Cerebral arteriography revealed thrombosis of the right sylvian artery. Bilateral cerebral haemorrhage occurred after cranial trauma at 10 years of age. Hydroxyurea was begun in 1990. Facial palsy occurred in 1993. Systemic hypertension, which appeared in 1998, normalised with nicardipine. An acute chest syndrome occurred in March 1998. He was admitted to hospital in July 1998 for bilateral lower limb weakness, more pronounced on the left. Blood pressure was normal. Haemoglobin was 122 g/l, 20 g above the usual level before hydroxyurea treatment. Cerebral magnetic resonance imaging (MRI) performed in the days after the neurological event and repeated three months later were unchanged, and spinal MRI results were normal. Hydroxyurea was stopped for some weeks, in view of the raised haemoglobin concentration. The final decision was to restart hydroxyurea treatment in this patient suffering from multiple visceral complications of sickle cell disease.

ADVERSE EVENTS THAT DID NOT LEAD TO CESSATION OF TREATMENT

Seven children developed melanonychia. Three complained of headaches at the beginning of hydroxyurea treatment, two of drowsiness. One child reported moderate alopecia. A 17 year old girl reported secondary amenorrhoea, but decided to continue treatment.

Discussion

Hydroxyurea is the first drug that specifically decreases the frequency and severity of painful crises in sickle cell disease in children. A decrease in the severity of painful crises was reported by all but six of the 101 children with sickle cell disease studied, after an initial improvement in five of these six. No significant difference in growth velocity had been reported in the initial group of 35 children and adolescents.[4] A recent report of the effect of hydroxyurea on the growth of young mice[11] led us to pay special attention to the growth curves of the 13 children included before they were 5 years old; they were not affected by hydroxyurea use (mean (SD) follow up in this subgroup, 24 (9.9) months; range, 7–41) (table

Table 3 Weight for age and height for age Z scores in 13 children who began treatment with hydroxyurea before they were 5 years old

	At inclusion	*Under treatment*
Weight for age	+ 0.11	+ 0.53
Height for age	+ 0.40	+ 0.42

Mean (SD) follow up, 24 (9.9) months.
Z score = (actual anthropometric value - median reference value)/standard deviation.
Reference values from the French growth reference curves.

3). The only alternative to hydroxyurea in treating severe forms of sickle cell disease is recurrent transfusion, with its own potential complications, or bone marrow transplantation, which carries a 10% risk of death.[12] It is reasonable to hope that hydroxyurea might prevent some of the devastating complications of the disease, but the question of long term tolerance remains unanswered. Studies exploring its potential leukaemogenic effect have been carried out in diseases involving an intrinsic risk of leukaemic transformation,[13 14] which is not the case in sickle cell disease. On the other hand, leukaemia was diagnosed after at least three[14] or four[13] years of treatment. We have too few children with sufficiently long follow up to be certain of safety, because only 36 have been treated for more than three years. In our opinion, acute lymphoblastic leukaemia in one of our cohort was not associated with hydroxyurea. The time between the start of treatment and diagnosis of leukaemia was short, 1.5 months, and the type of leukaemia was not typical of secondary malignancy. Most likely, the exacerbation of pain that led to treatment with hydroxyurea was the first manifestation of the leukaemia. Nonetheless, we think that hydroxyurea treatment should remain a therapeutic option restricted to the most severe forms of sickle cell disease, to be given only for indications in which its efficacy has been proved, namely prevention of pain and acute chest syndromes.

Hydroxyurea was temporarily stopped in a 17 year old patient because the treatment had provoked a 20 g/l increase in haemoglobin. There have been other reports of the occurrence of strokes in spite of hydroxyurea treatment, arguing against a protective effect of the drug on neurological complications.[1 5 15] Furthermore, the influence of this rise in haemoglobin was discussed when the patient suffered an ischaemic neurological event, namely thrombosis of the right sylvian artery. Increased haemoglobin concentrations contribute to increased blood viscosity, which might alter cerebral blood flow and reduce oxygen delivery. This point is important in the follow up of children receiving hydroxyurea, because all series demonstrate a rise in haemoglobin concentrations during treatment, which can reach 20 or 30 g/l. Cerebral artery narrowing could be systematically sought by performing transcranial Doppler ultrasonography before instituting hydroxyurea treatment.

The discrepancy between the high rate of transient haematological toxicity seen in the HUG-KIDS study[6] and in our cohort might be related to the different frequencies with which blood counts were monitored, every two weeks in the HUG-KIDS study, every month in ours.

An unexpected finding of our study is the high number of patients in whom treatment was stopped. Fifteen of the first 35 children reported are no longer receiving hydroxyurea, in seven patients for reasons unrelated to a medical contraindication. Although efficacy is not a primary end point of our study, it should be noted that six of these interruptions were related to the reappearance of recurrent painful crises, after an initial benefit in five patients. This deserves further study: are the effects of the drug exhausted after some years in some patients? If so, do these patients share any particular characteristics and why does this happen?

We conclude that hydroxyurea did not induce any pronounced toxicity in a cohort of 101 children with sickle cell disease followed for a median of 22 months. We reserve its use for the most severe forms of the disease because of continuing uncertainties about long term tolerance. Furthermore, we suggest that haemoglobin rises must be carefully controlled, and advise phlebotomies in those whose haemoglobin concentration exceeds 110 g/l.

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